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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HMJ03257WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03773	02/10/2000	01/10/1999
International Patent Classification (IPC) or national classification and IPC A61K9/127		
Applicant LIPOXEN TECHNOLOGIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/03/2001	31.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mennessier, T Telephone No. +49 89 2399 8687

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03773

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16 as originally filed

Claims, No.:

1-20 with telefax of 16/01/2002

Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-20.

because:

   ☒ the said international application, or the said claims Nos. 16 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 10 (as a whole); 11-18 and 20 (each partly) are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☒ the claims, or said claims Nos. 1 and 19 (as a whole); 8-12 and 14-20 (each partly) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 2-8, 11-18 and 20	(see point 3(a) of the separate sheet)

	No:	Claims		
Inventive step (IS)	Yes:	Claims	2-8, 11-16 and 20	(see point 3(a) of the separate sheet)
	No:	Claims	17 and 18	(see point 3(a) of the separate sheet)
Industrial applicability (IA)	Yes:	Claims	2-8, 11-15, 17, 18 and 20	(see point 3(a) of the separate sheet)
	No:	Claims		

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Comments with respect to item I

According to **claim 1 and claim 19**, at least 50% by mole of the zwitterionic phospholipid has the formula II.

It appears that no support exists in the application as originally filed for such a broad technical feature which attempts to include any percentage from 50% to 100%. In this respect, it is worth noting that the statement at lines 25-26 of page 4 according to which "*Preferably the proportion of groups R3 and R4 which are saturated in a mixture is at least 50%*" does not mean that, as referred to in claims 1 and 19, "*at least 50% by mole of the zwitterionic phospholipid[s] has the formula II*", for the reason that in said statement said groups are globally taken into consideration whatever they are part of the same zwitterionic phospholipid or of different zwitterionic phospholipids (as expressed in formula II of page 2 according to which R3 and R4 are the same or different with f equal to 0 to 6).

The only existing support is for the percentage 100%. It is provided by the liposome preparation referred to at lines 20-22 of page 9. Indeed, in said preparation, that furthermore is such that the cationic compound and the zwitterionic phospholipid are in a molar ratio of 1:4 (8 µmoles of DOTAP to be compared with 32 µmoles of DSPC), DSPC, which has the general formula II, is the only component being a zwitterionic phospholipid.

In respect of the other liposome preparations also referred to in the experimental part, it has to be noted that none of them are encompassed by the definition given in either of **claims 1 and 19**, as the cationic compound(s) and the zwitterionic phospholipid(s) of said preparations are in a molar ratio which is not comprised within the range 1:1 to 1:5.

In view of the above comments, the amendment "at least 50% by mole" has been taken into account in the present report, only insofar as the requirements of Rule 70(2)(c) PCT are met, i.e., insofar as 100% by mole of the zwitterionic phospholipid has the general formula II.

2. Comments with respect to item III

a) Industrial applicability

Claim 16 is directed to a method of treatment of the human or animal body by therapy, i.e., relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

b) Lack of clarity

As the index "f" used in **claim 10** has no antecedent in any of the preceding claims, the subject-matter of said claim appears not to be clearly defined. The objection extends to **claims 11-18 and 20**, insofar as their subject-matter is defined with a back-reference to claim 10. The defect is such that no opinion will be formulated as to novelty, inventive step and industrial applicability with respect to claim 10, as a whole, and claims 11-18 and 20, each partly.

c) Inadequate support

An adequat support appears to exist only for a vaccine of which the cationic compound is structurally defined as in either of present claims 2 and 13. In this respect, the point has to be stressed that from the experimental results presented in the description a person skilled in the art could not inferred that the favourable immunisation experiments reported in the application could also be reproduced using a vaccine containing any other cationic compound(s). The defect is such that no opinion will be formulated as to novelty, inventive step and industrial applicability with respect to (i) **claims 1 and 19**, each as a whole, and (ii) **claims 8-12, 14-18 and 20**, each partly, i.e., insofar as the cationic compound is as defined in claim 1.

3. Comments with respect to item V

a) Preliminary remarks

In view of the comments made at points 1 and 2(b) above, the following comments regarding novelty, inventive step and industrial applicability are made with respect to **claims 2-9, 11-18 and 20**, each only partly, in that an opinion is formed only with respect to (i) those embodiments according to which 100% by mole of the zwitterionic phospholipid has the general formula II as defined in claim 1 and the cationic compound is as defined in either of claims 2 and 13, (all claims concerned) and (ii) insofar as the subject-matter of claims 11-18 and 20 is not defined with a back-reference to claim 10.

b) Cited documents

(i) Reference is made to the following documents which are cited in the international search report:

D1: *Methods*, 19(1), 1999 September, 156-62
D2: *J. Pharm. Pharmacol.*, 50(suppl., British Pharmaceutical Conference), 1998, 103
D3: WO 98/10748
D4: *FEBS Letters*, 402 (1997), 107-110

Both inventors appears to have contributed to each of documents D1 and D2. One of the inventor also appears to be the (only) inventor who has been designated with respect to document D3. The same inventor appears to have contributed to document D4.

(ii) Document D1 reports on vaccine entrapment in liposomes. Entrapment of plasmid DNA is carried out by the dehydration-rehydration procedure of **claim 17** and also includes a microfluidisation as proposed in **claim 18** (see D1, pages 159-160). The following vaccine compositions have been used (see D1, Table 2 on page 158) which each includes both a cationic compound and a zwitteronic phospholipid in conjunction with a

glycerolipid to prepare the liposomes:

PC, DOPE, BisHOP
PC, DOPE, DOTMA
PC, DOPE, DC-Chol
PC, DOPE, DOTAP
PC, DOPE, DODAP

(iii) Document D2 reports on genetic immunization using liposome-incorporated DNA. Plasmid pRc/CMV HBS was entrapped by the dehydration-rehydration method (see claim 17) in liposomes composed according to preferred embodiments of:

PC:DOPE:DOTAP
DSPC:DOPE:DOTAP

Mice were given intramuscular injections of the said vaccines.

(iv) Document D3 (see claim 13 and Tables 3, 4, 5 and 7 on pages 25, 26, 27 and 34 of the experimental part) discloses vaccine compositions comprising a nucleic acid operatively encoding an antigen complexed with or entrapped within liposomes forming components including a cationic component having the general formula represented in claim 9 (of D3) and at least one fosugenic lipid.

A preferred cationic component is "DOTAP". According to claim 12 and page 10, lines 3-5, the fusogenic lipids are phosphatidyl ethanolamines in which the acyl groups are unsaturated, of which one of them, referred to as "DOPE" (dioleoyloxy phosphatidyl ethanolamine) is mentioned in the examples. In addition to said phosphatidyl ethanolamines, phosphatidylcholines can also be used. One of them, "DSPC" (distearoyloxy phosphatidylcholine) has been employed to prepare one of the preferred vaccine compositions of D3.

Indeed, among the preferred vaccine compositions of document D3,

one can cite the following two ones:

PC:DOPE:DOTAP [see Tables 3, 4, 5 and 7 on pages 25, 26 ,27 and 34, respectively]

DSPC:DOPE:DOTAP [see Table 7 page 34]

Document D3 (see claims 29 and 30) also refers to a method of entrapping polynucleotide into cationic liposomes comprising the same steps as those of the method to which present **claim 17** is directed.

(v) Document D4 appears to be at least for some aspects of the work reported therein a non-patent literature counterpart of document D3. A PC:DOPE:DOTAP preparation is tested.

c) Novelty (Article 33(2) PCT)

As the liposome components of the vaccines of the present invention as defined in the claims, in terms of their respective ratios and compositions, are not disclosed in the cited prior art documents, the claimed subject-matter as defined at point 3(a) above can be acknowledged as new.

d) Inventive step (Article 33(3) PCT)

(i) Claims 2-9, 11-16 and 20

As it is considered that a person skilled in the art could not have inferred from the teaching of the cited prior art documents when taken into consideration alone or in combination that a vaccine as referred to in **claims 2-9, 11-16 and 20** would be efficient upon oral administration, it can be acknowledged that the subject-matter of said claims as defined at point 3(a) above involves an inventive step.

(ii) Claims 17-18

In view of the comments made at points 3(b)(ii) and 3(b)(iv), it has to be considered that a person skilled in the art would have regarded it as obvious to entrap a polynucleotide into liposomes as defined in the present claims using the methods of documents D1 (for claims 17 and 18) and D3 (for claim 17). Therefore, the subject-matter of **claims 17 and 18,** as defined at point 3(a) above, cannot be considered to involve an inventive step.

e) Industrial applicability (Article 33(4) PCT)

(i) It may be considered that the subject-matter of **claims 2-9, 11-15 and 17-18 and 20** is susceptible of industrial applicability.

(ii) For the assessment of (a) the present **claim 16** and, (b), to some extent, the present **claim 20** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject- matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Comments with respect to item VIII

In view of the comments made at point 2 above, the subject-matter of **claims 1 and 8-20** has to be objected to under Article 6 PCT.